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EDITORIAL

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The further development of out-of-office BP monitoring: Japan's ImPACT Program Project's achievements, impact, and direction

1 | INTRODUCTION

New guidelines for the management of hypertension were recently released by the European Society of Hypertension/European Society of Cardiology (the 2018 ESH/ESC guidelines) and the American College of Cardiology/American Heart Association (the 2017 ACC/AHA guidelines).[1,2] These guidelines stress the importance of out-of-office blood pressure (BP) values over that of office BP values. In Japan and other Asian countries, we have highlighted the use of the out-of-office BP-guided management of hypertension.[3-5] Ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) are the two standard measurements of out-of-office BP. Their use can detect masked (uncontrolled) hypertension (normotension in office BP and hypertension in out-of-office BP) in individuals at the highest risk of cardiovascular events.[6-8] There are three clinical phenotypes of masked hypertension: morning hypertension, daytime hypertension, and nocturnal hypertension.[9]

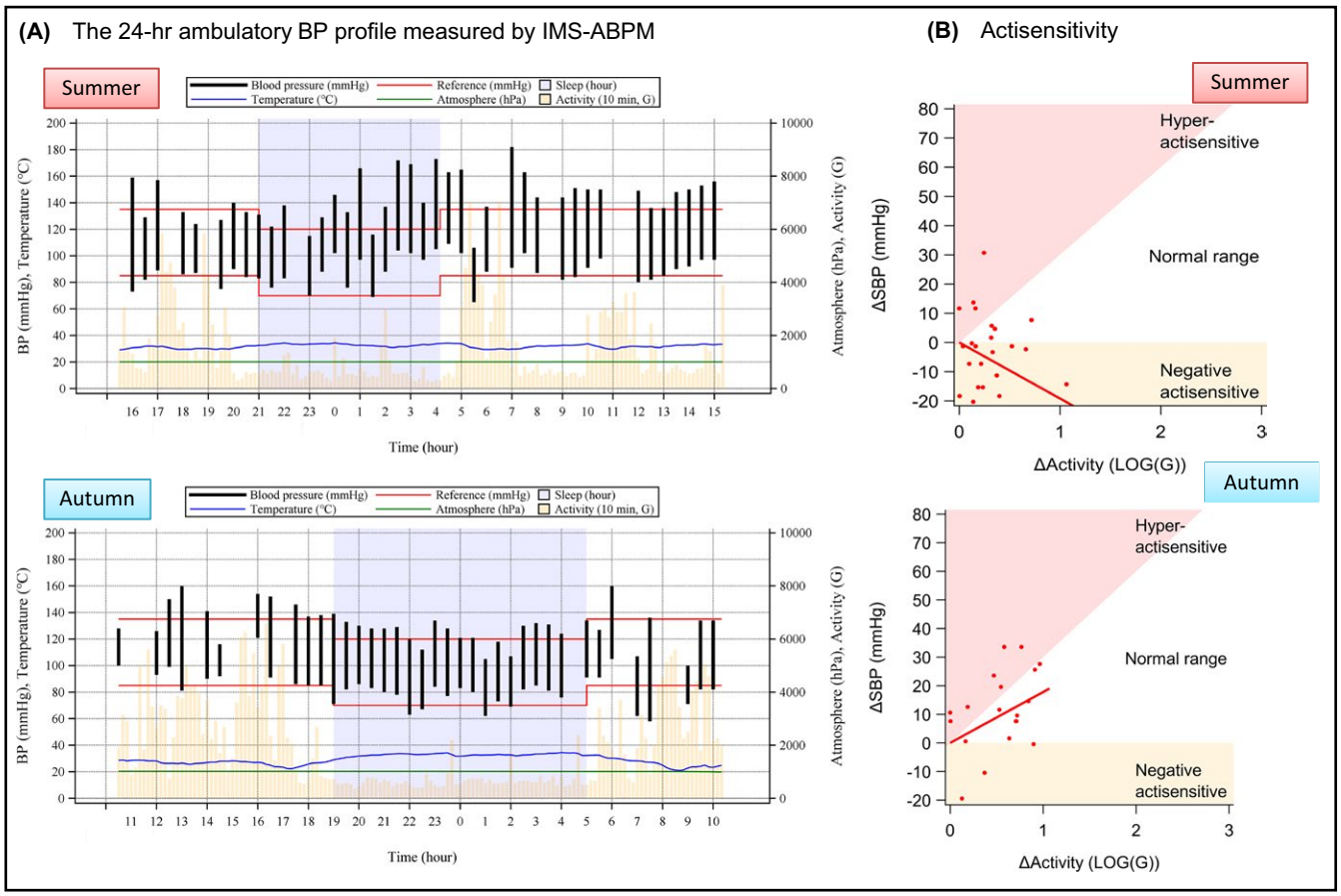

FIGURE 1 Abnormal 24-h ambulatory BP profiles and actisensitivity in a 72-y-old woman who developed B-type aortic dissection during the daytime. A, The 24-h trend of ambulatory BP and the parameters measured by IMS-ABPM *Upper*: The riser pattern was detected in summer (8 mo before onset). *Lower*: An excessive morning surge was detected in autumn (4 mo before onset). B, Actisensitivity calculated as the slope of daytime ambulatory BP change against the physical activity change. The red plots and the regression line represent the data of 72-y-old woman who developed aortic dissection. *Upper*: The inverse actisensitivity was found in summer. *Lower*: The actisensitivity was within the normal range

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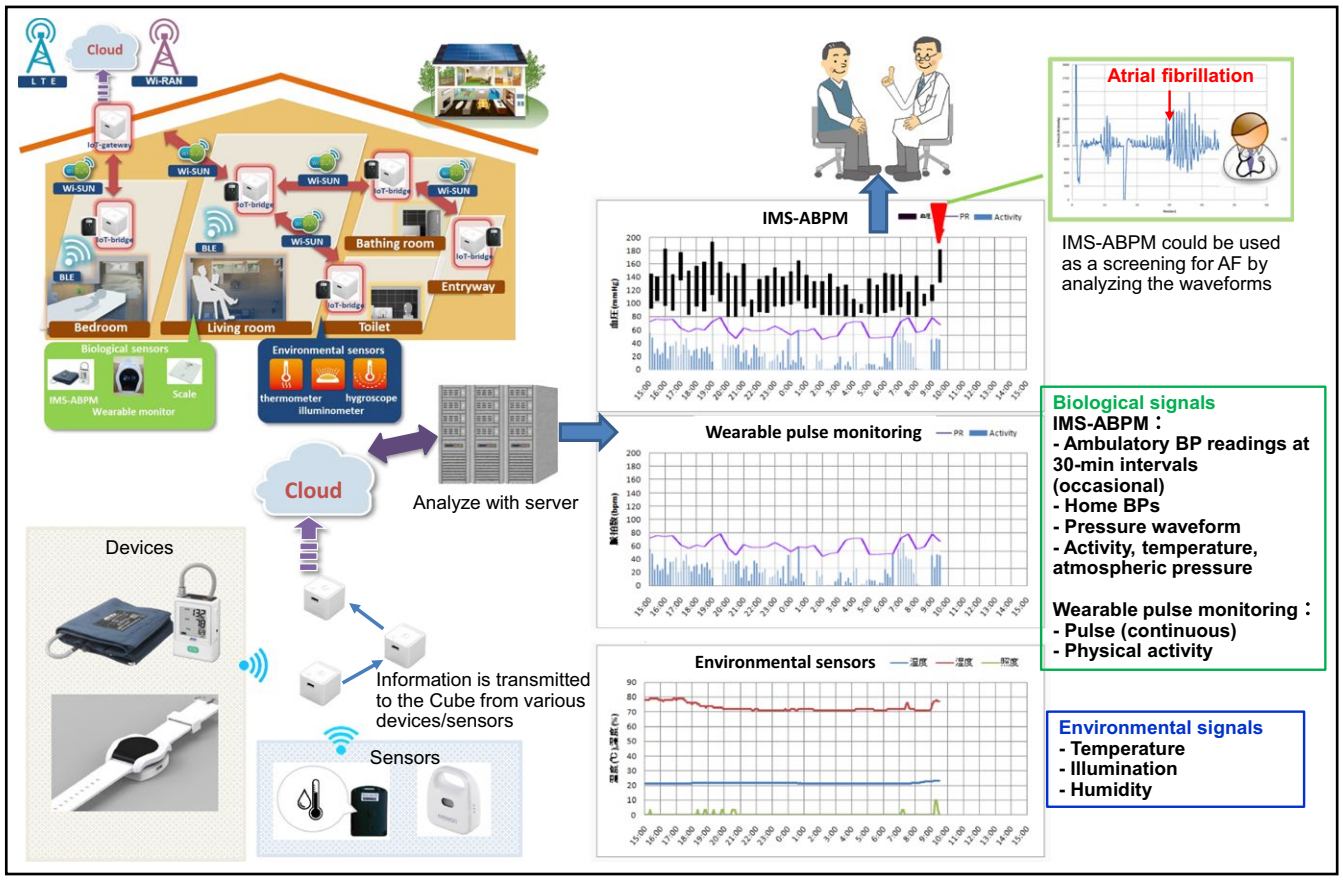

FIGURE 2 A novel approach to individual management for hypertension. Biologic and environmental signals corresponding to an individual's living conditions at home were simultaneously collected from multiple devices and sensors by an IoT (Internet of Things) gateway and bridges based on the hybrid Wi-SUN/Wi-Fi transmission system. This high-speed analysis and reporting system facilitates hypertensive management. (http://www.jichi.ac.jp/usr/card/research/index_en.html). BLE, Bluetooth®

Ambulatory BP monitoring has traditionally been considered the gold standard to detect the risk of high BP throughout the 24-hour day, and its use can detect all three types of masked hypertension. Toward the achievement of the goal of "zero" cardiovascular events, three components are needed for "perfect 24-hour BP control": (a) lowering the 24-hour BP level, (b) maintaining an adequate circadian rhythm, and (c) avoiding excessive BP variability including the morning BP surge.[10] All three of these components can be assessed by ABPM. Extremely disrupted patterns of circadian rhythm of nighttime BP and exaggerated morning BP surge such as the riser pattern (higher nighttime BP than daytime BP) and the extreme-dipper pattern (excessive nighttime BP falls) are reported to be associated with cardiovascular risk.[11-13]

Home BP monitoring is frequently used in clinical practice and to identify masked hypertension defined by self-measured home BP. The use of HBPM can detect the risk of morning hypertension.[14-18] The recently developed "nighttime HBPM" automatically obtains and records BP values at fixed intervals while an individual is sleeping, and it can be used as an alternative to ABPM for the assessment of nighttime BP.[13] Two additional modalities have been developed to detect the risk of hypertension during sleep (especially in patients with obstructive sleep apnea): (a) "trigger nighttime HBPM" with a hypoxic episode-trigger function and a heart rate-trigger function and (b) beat-by-beat continuous surge BP monitoring.[13,19]

Home BP monitoring can thus detect the risk of morning hypertension and that of nocturnal hypertension. However, HBPM would underestimate the risk of daytime hypertension, because HBPM measures an individual's blood pressure in the less stressful resting condition at home. A patient's behavior, surrounding environment, and various triggering factors affect his or her daytime ambulatory BP changes. Masked daytime hypertension (ie, normotension in office BP and hypertension in daytime BP) induced by physical activity or work- or home-related psychological stress can be detected only by ABPM.

2 | NEW MULTI-SENSOR ABPM AND BP SENSITIVITY INDEXES

We recently developed a device that provides information/communication technology (ICT)-based multi-sensor ABPM (IMS-ABPM), which can store all of the waveforms of intra-cuff pressures during oscillometric BP measurement.[20] One of the limitations of the original ABPM is the accuracy of "real" daytime BP measurements, because the daytime movement of the ABPM device wearer's upper arm may

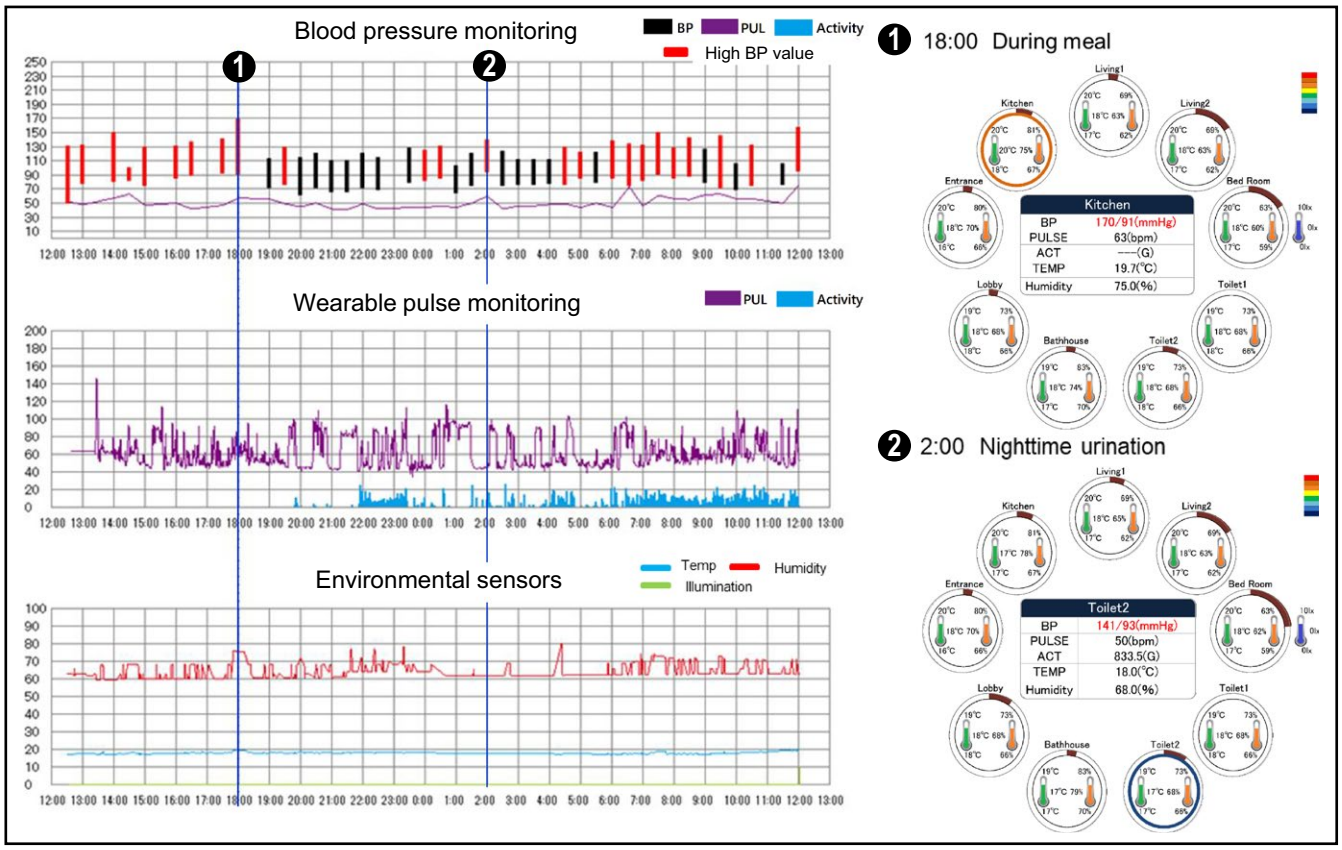

FIGURE 3 Time-trend reporting system of ambulatory BP and environmental conditions along with an individual's high-risk places and times

modify the intra-cuff pressure and produce BP reading artifacts. By excluding the abnormal BP values with abnormal waveforms as artifacts, we can evaluate the "real" daytime BP measurements more accurately. In addition, based on the IMS-ABPM's stored waveforms and its function of detecting an irregular heartbeat (IHB),[21] the device can be used for the screening of atrial fibrillation (AF).

The IMS-ABPM device is equipped with a thermosensor, a highly sensitive actigraph, and an atmospheric pressure sensor to simultaneously assess the triggers of BP surge (a pressor component of BP variability).[20] By determining the association between many subjects' BP measurements and these triggers, new BP sensitivity indexes could be calculated; for example, the slope of the ambulatory BP values against specific triggers such as temperature (thermosensitivity evaluation), physical activity (actisensitivity), atmospheric pressure (atmospheric sensitivity), humidity (humidity sensitivity), and more. Based on these new indicators, we could classify the characteristics of hypertension with excessive BP sensitivity to specific triggers such as thermosensitive hypertension, actisensitive hypertension, atmospheric hypertension, and humidity-sensitive hypertension. These sensitivities might overlap and augment each other.

In fact, the actisensitivity of BP (the slope of daytime BP change against physical activity change during a 5-minute period before the BP measurement) is augmented in the cold winter season compared to the warm summer in the same patients.[22] This may partly explain the winter increase in the rate of cardiovascular events. The IMS-ABPM device can specifically detect masked daytime hypertension with a physical activity-induced BP surge.

As an example: a 72-year-old woman developed B-type aortic dissection during the daytime. Although she had been treated with amlodipine, candesartan, and hydrochlorothiazide, the IMS-ABPM device detected abnormal 24-hour BP profiles during the year prior to the onset of aortic dissection. The riser pattern was detected in the summer (8 months before the onset), and an excessive morning surge was detected in the autumn (4 months before the onset) (Figure 1A). The patient's simultaneously calculated actisensitivity was also disrupted. The actisensitivity was within the normal range in autumn; however, the inverse actisensitivity (physical activity reduced the ambulatory BP) was found in summer (Figure 1B). The disrupted BP regulation against physical activity, which is modified by environmental (eg, seasonal) conditions, might produce the excessive BP surge that triggers cardiovascular events.

3 | THE IMPACT HYBRID WI-SUN/WIFI TRANSMISSION SYSTEM

Based on recent technology developments, it has been suggested that the use of ICT-based devices and a real-time feedback IoT (Internet of Things)-based system could facilitate a novel approach to patient management.[22,23] In the ImPACT program (IMpulsing PAradigm Change

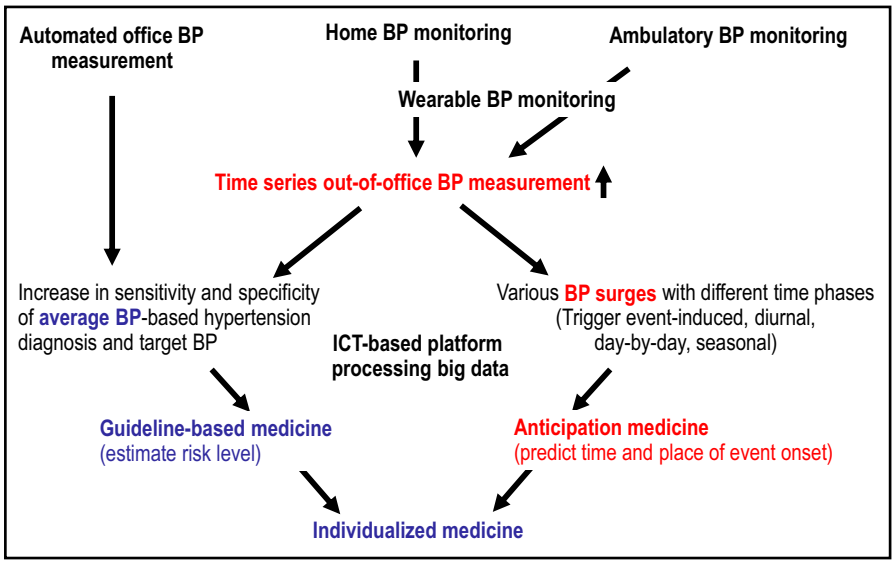

FIGURE 4 Time series out-of-office BP-based anticipation management of hypertension: Effective for bridging the gap between the guidelines and individualized medicine

through disruptive Technologies program of the Cabinet Office, Government of Japan), we have successfully developed an integrated system that collects both biologic and environmental data, with the hybrid Wi-SUN/Wi-Fi transmission system (Figure 2). Environmental sensors introduced in a patient's home continuously monitor the temperature, humidity, and illumination in different rooms with different conditions throughout 24-hour periods. An ICT-based wrist-type pulse wave monitoring device (wearable monitoring) which we also developed in the ImPACT program continuously monitors the wearer's pulse rate, pulse wave, and activity.

With the combination of these biological sensor devices, environmental sensors, and the hybrid Wi-SUN/Wi-Fi transmission system, the environmental determinants of BP surges (ie, the pressor component of BP variability) with different time phases could be used to identify the riskiest places and times at which an individual's maximum BP surge is exaggerated at home throughout the year (Figure 3). Health information technology (HIT) solutions like this are increasingly being recognized as an important component of the advances in health care, and the latest version of the ACC/AHA hypertension guidelines highlight the importance and emerging roles of HIT.[1]

4 | BLOOD PRESSURE SURGE-BASED ANTICIPATION MEDICINE

Using these new technologies, it is hoped that the occurrence of cardiovascular events could be anticipated based on data obtained by these novel approaches to out-of-office patient monitoring, with the ultimate goal of eliminating the occurrence of cardiovascular events in patients with hypertension. Such an approach is referred to as "anticipation medicine" for zero cardiovascular events, within which BP variability is a key biomarker.[10,19,20,22] The self-monitoring of blood pressure using HBPM, particularly when combined with telemonitoring, has recently been shown to facilitate the titration of antihypertensive therapy in subjects with poorly controlled hypertension in general practice, without increasing the general practitioner's workload.[24,25] This highlights the potential for ICT-based out-of-office BP measurement solutions in clinical practice.

There is a gap between the guideline-initiated general management of hypertension and the individualized optimal management of hypertension. An increase in the number of out-of-office BP measurements could increase the sensitivity and specificity of the average BP-based diagnosis of hypertension (as guideline-based medicine), and this increase in data could also detect the various specific trigger-induced BP surges, that is, diurnal, day-by-day, and seasonal BP surges (as individualized medicine) (Figure 4). The resonance hypothesis holds that the exaggerated pathological surge BP generated by the resonance of different BP surges with different time phases would trigger cardiovascular events.[26] The times and places at which the surge BP is generated would be the most risky times/places for an individual's cardiovascular event onset. Even among well-controlled hypertensive patients, the morning BP surge remains significant in the winter.[27] Anticipation medicine for cardiovascular diseases—which both anticipates pathological surge BP based on the previous time series of individual BP data and avoids the generation of surge BP—is an ideal future practical direction to take in order to decrease the gap between the guidelines and individualized medicine in the era of ICT-based "real-world" big data analysis and feedback systems.

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CONFLICT OF INTEREST

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